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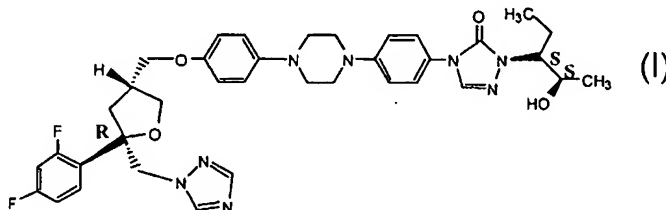
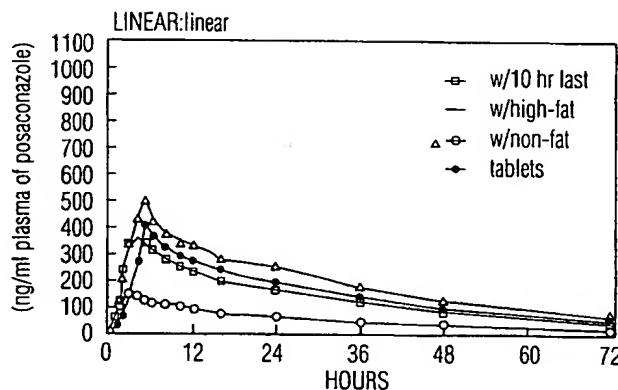
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(54) Title: ANTIFUNGAL COMPOSITION WITH ENHANCED BIOAVAILABILITY



(57) Abstract: A liquid suspension comprising an antifungally effective amount of the micronized compound represented by the chemical structural formula (I) at least one thickening agent, a non-ionic surfactant, and a pharmaceutically acceptable liquid carrier is disclosed.



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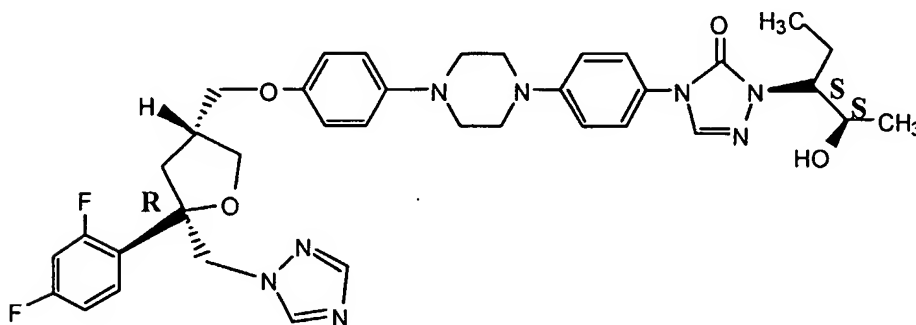
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ANTIFUNGAL COMPOSITION WITH ENHANCED BIOAVAILABILITY

BACKGROUND OF THE INVENTION

This invention relates to stable, liquid suspensions containing an antifungally effective amount of the micronized compound represented by the chemical structural formula I:



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at least one thickening agent, a non-ionic surfactant, and a pharmaceutically acceptable liquid carrier, and methods of using the suspensions to treat or prevent fungal infections

10 U.S. Patent No. 5,661,151 discloses the compound of formula I and its potent antifungal activity against a broad range of fungi such as *Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, and other opportunistic fungi.

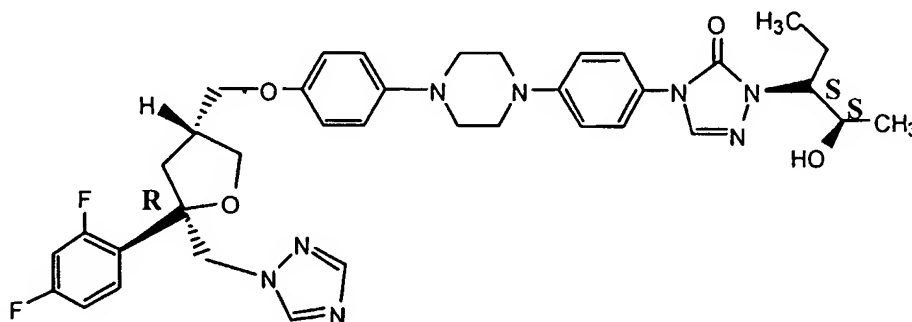
U.S. Patent Nos. 5,834,472 and 5,846,971, disclose oral pharmaceutical capsule compositions of the compound of structural formula I coated onto inert
15 beads together with a binder. However, the compound of structural formula I is highly lipophilic, and has an extremely low water solubility. Thus, aqueous compositions of the compound of structural formula I were found to have reduced

anti-fungal activity and/or bioavailability, presumably due to the extremely low water solubility of the compound. Accordingly, a need exists for an oral pharmaceutical composition of the compound of structural formula I that has enhanced bioavailability and improved stability characteristics

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SUMMARY OF THE INVENTION

We have found pharmaceutical compositions, in the form of liquid suspension, suitable for oral administration comprising micronized particles of posaconazole, the compound having the chemical structural formula I

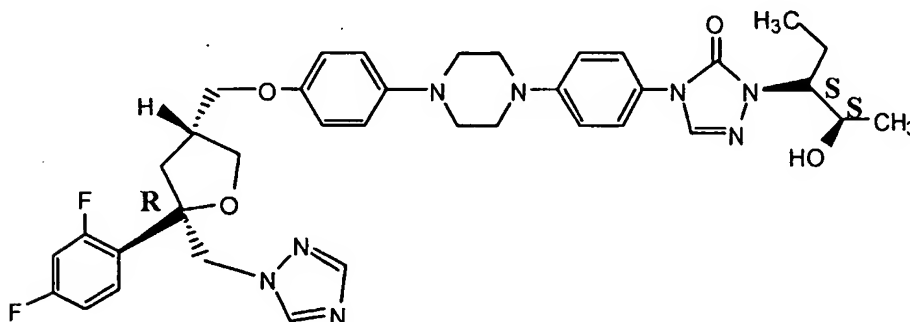


10 at least one thickening agent, a non-ionic surfactant, and a pharmaceutically acceptable liquid carrier that provides significant advantages over the prior art.

Advantages of the liquid suspensions of the present invention include improved homogeneity of the suspension and ease of dispersibility of the suspension. The solids that settle in the liquid suspension of the present invention
 15 do not form a solid cake that is difficult to re-disperse. There is virtually no sedimentation of the solids in the unreconstituted liquid suspension of this invention for a period of at least three days. This surprising feature ensures that a patient having a fungal infection taking the liquid suspensions of the present invention will receive an antifungally effective amount of posaconazole. The liquid suspensions

of the present invention have a longer shelf life. Additionally, the liquid suspension, upon reconstitution, provide substantially the same antifungally effective amount posaconazole as the initially prepared suspension. These features of the liquid suspensions of the present invention provide benefits to pharmacies, pharmacists, 5 doctors and patients having fungal infections.

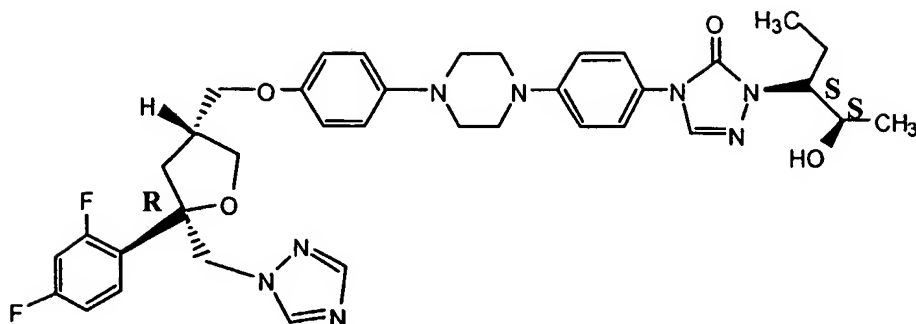
Accordingly, the present invention provides a liquid suspension comprising micronized posaconazole, having the chemical structural formula I:



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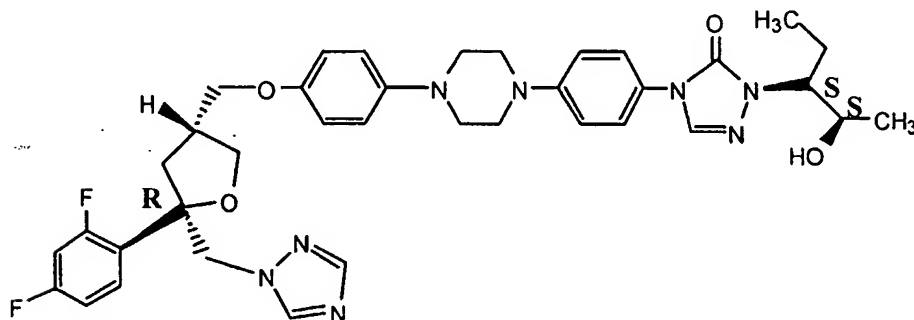
at least one thickening agent, a non-ionic surfactant, and a pharmaceutically acceptable liquid carrier.

This invention also provides a liquid suspension comprising an antifungally effective amount of micronized posaconazole having the chemical structural 15 formula I:



an effective amount of at least one thickening agent, an amount of a buffer system effective to maintain the pH of the system in the range of about 4.0 to about 6.0, an effective amount of a non-ionic surfactant, and a pharmaceutically acceptable liquid carrier.

This invention further provides a liquid suspension comprising an antifungally effective amount of micronized posaconazole having the chemical structural formula I:



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wherein the micronized compound has a mean particle size in the range of about 1200 nm to about 1600 nm, an effective amount of polyoxyethylene derivatives of

sorbitan esters of saturated or unsaturated C₁₂ to C₁₈ acids, an effective amount of a buffer system sufficient to maintain a pH in the range of about 4.0 to about 6.0, an effective amount of a combination of two thickening agents, wherein one is a liquid sugar, and a pharmaceutically acceptable liquid carrier.

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BRIEF DESCRIPTION OF THE FIGURES

Figures 1 & 2 graphically display the mean plasma concentration time profiles of posaconazole tablets and of the liquid suspension of Example 1 of the present invention. Figure 1 is a linear:linear graphic profile of the plasma concentration (ng/ml) of the compound of formula I versus time (hours) after administration of the
10 following four **Treatments A- D**: a single of 2 x 100 mg of the compound of formula I in the tablet co-precipitate formulation of U.S. Patent No. 5,834,472 with a standardized high-fat breakfast- **Treatment D** and. symbol --; a 200 mg of the compound of formula I in the oral suspension of this invention (5 ml) following a 10-hr. fast -**Treatment A** and. symbol -0-; a 200 mg of the compound of formula I in the
15 oral suspension of this invention (5 ml) with a standardized high-fat breakfast- **Treatment B** and. symbol - - ; and a 200 mg of the compound of formula I in the oral suspension of this invention (5 ml) with a standardized non-fat breakfast- **Treatment C** and. symbol- - .

Figure 2 is a log :linear graphic profile of the plasma concentration (ng/ml) of the
20 compound of formula I versus time in hours for the data presented in Figure 1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a stable suspension of micronized particles of the antifungal compound posaconazole in a pharmaceutically acceptable liquid

carrier. The suspension of the present invention is stable to settling without sedimentation when stored undisturbed for more than three days at 25°C. (See Table 1 below).

Table 2 below shows that the liquid suspension formulations of this invention
5 are stable in that the concentration of posaconazole in the suspension is substantially the same ($\pm 2\%$) compared to the initial concentration (as measured by HPLC) for periods of up to 12 months.

We have also found that the stable suspension of the present invention has a remarkably higher (23-36% increase) bioavailability compared to an optimized
10 oral tablet of micronized particles of posaconazole when each is administered to subjects concurrently with a high fat breakfast. See Tables 3 and 4 and Figures 1 & 2

One aspect of the present invention is to provide a pharmaceutical composition that contains micronized particles of posaconazole in combination with
15 a non-ionic surfactant, such as a sorbitan ester and at least one thickening agent, preferably a combination of xanthan gum and a liquid sugar, that are easily dispersible in a pharmaceutically acceptable liquid carrier such as purified water. The pharmaceutical composition provides a stabilized suspension that does not settle for at least three days, thus ensuring that patients will get an effective dose of
20 posaconazole. Another feature of the stabilized suspension of the present invention is that it is useful in treating patients with HIV-1 infections with oral thrush without posaconazole precipitating out of solution. Another aspect of the present

invention is that the suspension of the present invention avoids formation of solid cakes which are difficult to disperse.

The compound of formula I used in the suspensions of the present invention is available from Schering Corporation, Kenilworth, New Jersey , and has been
5 prepared according to Examples 24 and 32 of U.S. Patent No. 5,661,151 and WO 95/17407.

Micron-sized particles of posaconazole preferably have a mean particle size range of about 1000 nanometers (nm) to about 1800 nm, preferably about 1200 nm to about 1600 nm, and most preferably about 1400 nm. This particle size can be
10 obtained either by the final step during the manufacture of the antifungal compound of formula I or by the use of conventional micronizing techniques after the conventional crystallization procedure(s).

The preferred micronizing technique that is employed to micronize the posaconazole to the desired mean particle size range is microfluidization.
15 Microfluidization is an alternative to traditional homogenization that utilizes the collision of two product streams at high pressures to produce a much more uniform particle size distribution (according to Microfluidics International Co.) and smaller average particle size of about 1200 nm to 1600 nm. The process and equipment used in microfluidization are described in U.S. Pat. No. 4,533,254.

20 The micronized posaconazole of the present invention may also be present in crystalline form. It is preferably substantially chemically and optically pure, and it contains less than about 10 % of its optical isomers, enantiomers or other diastereomers. It may be 99% of the optically pure the levorotatory or

dextrarotatory isomer. This optically pure compound of chemical structure I should avoid many of the untoward side effects of a mixture of other optical isomers.

Posaconazole liquid suspension is employed in the composition in antifungally amounts effective to control the fungi of interest. Such antifungally effective amounts can range from about 10 mg/ml to about 100 mg/ml concentration of the liquid suspension formulations of the present invention, more preferably from about 20 mg/ml to about 60 mg/ml, and most preferably about 40 mg/ml of the compound of formula I.

The present invention also provides for a method of treating and/or preventing fungal infection in a mammal comprising administering to the mammal an amount of the liquid suspension containing the micronized posaconazole in an amount effective for treating and/or preventing such fungal infection. Antifungally effective amounts of liquid suspensions of present invention containing 40 mg/ml of the compound of formula I is administered orally in the doses of 5 ml - containing 200 mg of formula I - three times a day (TID) or four times a day (QID)- or 10 ml- containing 400 mg of the compound of formula 1-twice a day (BID). Of course, the attending clinician may change the dose and dosing regimen in view of the age, health, and sex of the patient as well as the severity of the fungal infection.

The following terms are used to describe the present pharmaceutical compositions, ingredients that may be employed in its formulation and methods for assessing the compound's bioactivity or bioavailability.

Non-ionic surfactant refers to a surfactant which lacks a net ionic charge and does not dissociate to an appreciable extent in aqueous media. The properties of non-ionic surfactants are largely dependent upon the proportions of the hydrophilic

and hydrophobic groups in the molecule. Hydrophilic groups include the oxyethylene group (-OCH₂CH₂-) and the hydroxy group. By varying the number of these groups in a hydrophobic molecule, such as an ester of a fatty acid, substances are obtained which range from strongly hydrophobic and water insoluble compounds, such as glyceryl monostearate, to strongly hydrophilic and water-soluble compounds, such as the macrogols. Between these two extremes types include those in which the proportions of the hydrophilic and hydrophobic groups are more evenly balanced, such as the macrogol esters and ethers and sorbitan derivatives. Suitable non-ionic surfactants may be found in Martindale, The Extra Pharmacopoeia, 28th Edition, 1982, The Pharmaceutical Press, London, Great Britain, pp. 370 to 379.

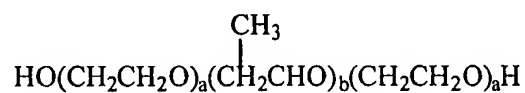
Such suitable non-ionic surfactants include block copolymers of ethylene oxide and propylene oxide, glycol or glyceryl esters of saturated or unsaturated C₈ to C₂₀ acids, preferably, polyoxyethylene esters of saturated or unsaturated C₈ to C₂₀ acids, polyoxyethylene ethers of saturated or unsaturated C₈ to C₂₀ acids, and polyvinylalcohols or sorbitan esters of saturated or unsaturated C₁₀ to C₂₀ acids. Preferably, the non-ionic surfactant is a sorbitan ester of a saturated or unsaturated C₁₀ to C₂₀ acid, and more preferably the sorbitan ester is a fatty acid ester of sorbitan selected from sorbitan monolaurate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, sorbitan monopalmitate, sorbitan monostearate and sorbitan tristearate, or mixtures thereof.

Suitable sorbitan esters include, e.g. Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 65, Polysorbate 80, Polysorbate 85, Sorbitan Monolaurate, Sorbitan Mono-oleate, Sorbitan Monopalmitate, Sorbitan

Monostearate, Sorbitan Sesquioleate, Sorbitan Trioleate and Sorbitan Tristearate.

The most preferred non-ionic surfactant is Polysorbate 80, available from ICI Americas under the tradename Tween 80 which is a mixture of oleate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester,
 5 condensed with approximately 20 moles of ethylene oxide.

Suitable block copolymers of ethylene oxide and propylene oxide generically called "Poloxamers" and include those represented by the following chemical structure I:



10 wherein a is an integer ranging from about 10 to about 110, preferably from about 12 to 101; more preferably from about 12 to 80; and

b is an integer ranging from about 20 to about 60, more preferably from about 20 to about 56; also from about 20 to 27.

Suitable glycol and glyceryl esters of fatty acids include glyceryl monooleate
 15 and similar water soluble derivatives;

Suitable polyoxyethylene esters of fatty acids (macrogol esters) include polyoxyethylene castor oil and hydrogenated castor oil derivatives;

Suitable polyoxyethylene ethers of fatty acids (macrogol ethers) include Cetomacrogel 1000, Lauromacrogols (a series of lauryl ethers of macrogols of
 20 differing chain lengths), e.g. Laureth 4, Laureth 9 and Lauromacrogol 400.

The effective amount of non-ionic surfactant in the composition can range from about 5 mg/ml to about 50 mg/ml concentration of the formulation, more preferably from about 5 mg/ml to about 25 mg/ml, and most preferably 10 mg/ml.

Thickening agents found suitable in the present invention include any commercially available agent useful for such purpose. Xanthan gum, liquid sugars, starches, celluloses and mixtures thereof are preferred thickening agents. More preferred is a combination of xanthan gum and a liquid sugar and, most preferred is a combination of xanthan gum, NF and glucose, NF. Preferably, the xanthan gum is present in an amount of about 1 mg/ml to about 5 mg/ml, and more preferably the xanthan gum is present in an amount of about 3 mg/ml. Preferably, the glucose NF is present in an amount of about 200 to about 500 mg/ml, and more preferably about 350 mg/ml. The effective amount of thickening agent of the present invention may be about 1 to about 500 mg/ml, more preferably about 200 to about 500 mg/ml, most preferably about 353 mg/ml. The thickening agents of the present invention facilitate suspension of the formulation after constitution with minimum agitation and prevent rapid settling and caking of the suspension over time.

Pharmaceutically acceptable carriers include those well known in the art, including purified water USP, liquid glucose, NF, and anhydrous glycerol. Most preferred is purified water USP and liquid glucose, NF. The pharmaceutically acceptable carrier may be present in an amount of about 10 to about 500 mg/ml, more preferably about 200 mg/ml to about 400 mg/ml, most preferably about 350 mg/ml.

The buffer systems suitable for the formulations of the present invention are those which maintain the pH of the liquid suspension in the range of about 4 to about 6, preferably in the 4.5 to 5.0, and most preferably about 4.5. The use of a buffer system of sodium citrate, USP and citric acid, USP, is preferred. Other suitable buffer systems may be used to maintain the desired pH range of 4 to 6.

The buffering agents may be present in a concentration of about 0.4 to about 1.5 mg/ml, more preferably about 0.7 to about 1.5 mg/ml, most preferably about 1.1 mg/ml.

Anti-foaming agents found suitable in the present invention include any
5 commercially available agent useful for such purpose including the methylated linear siloxane polymers end blocked with trimethylsiloxyl units such as dimethicone and simethicone, as well as mixtures of dimethicone with an average chain length of 200 to 250 dimethylsiloxane units and silica gel. The effective amount of anti-foaming agents is an amount sufficient to provide a concentration of
10 about 2 mg/ml to about 4 mg/ml, preferably about 3 mg/ml.

The water soluble preservatives found useful in present invention include sodium benzoate, sodium citrate and benzalkonium chloride as well as other pharmaceutically acceptable water soluble preservatives. Use of sodium benzoate as a preservative is preferred. The effective amount of the water soluble
15 preservative is an amount sufficient to provide a concentration of about 0.5 mg/ml to about 3 mg/ml, most preferably about 2 mg/ml.

The opacifier agents found suitable in the present invention include pharmaceutically acceptable metal oxides, especially titanium dioxide. The effective amount of the opacifier agent is an amount sufficient to provide a
20 concentration of about 2 mg/ml to about 6 mg/ml, most preferably about 4 mg/ml.

Typical flavoring agents are those that are approved by FDA for use in sweetened pharmaceuticals, foods, candies, beverages and the like; these materials impart flavors such as grape, cherry, citrus, peach, strawberry, bubble gum, peppermint and many others. The effective amount of the flavoring agents is

an amount sufficient to provide a concentration of about 0.01 mg/ml to about 6 mg/ml, more preferably about 5 mg/ml.

The following examples describe compositions of the present invention containing posaconazole, but they are not to be interpreted as limiting the scope of the claims.

<u>Ingredient</u>	<u>Concentration Range</u> (mg/ml)
Posaconazole (micronized)	10-100
Polysorbate 80	5-50
Sodium Citrate, USP, Monohydrate	0.4-0.8
Citric Acid, USP, Monohydrate	0.36-0.6
Simethicone, USP	2-4
Xanthan Gum, NF	1-5
Sodium Benzoate, NF	0.5-3
Liquid Glucose, NF	200-500
Glycerin, USP	50-150
Artificial Cherry Flavor	2-10
Titanium Dioxide	2-6
Purified Water, USP q.s. ad	---

The above ranges of ingredients may be varied as is evident to one skilled in the art.

Specific examples of a composition within the scope of the invention is set forth below.

Example 1

<u>Ingredient</u>	<u>Concentration</u>
	(mg/ml)
Posaconazole (micronized)	40
Polysorbate 80	10
Sodium Citrate, USP, Monohydrate	0.6
Citric Acid, USP, Monohydrate	0.48
Simethicone, USP	3
Xanthan Gum, NF	3
Sodium Benzoate, NF	2
Liquid Glucose, NF	350
Glycerin, USP	100
Artificial Cherry Flavor	5
Titanium Dioxide	4
Purified Water, USP q.s. ad	1ml

This example is prepared as follows: charge approximately 5% of the final batch volume of purified water at $20 \pm 3^{\circ}\text{C}$ to a suitable vessel equipped with a mixer propeller. Add 40% of the polysorbate 80 to the purified water in step 1 and mix until dissolved. Add 40% of the simethicone and mix until it is dispersed.

- 5 Recirculate the mixture in step 3 through a Microfluidizer, operating at about 30,000 \pm 5000 psi for approximately 5 passes. Add approximately 7% of the final batch volume of purified water at about $20 \pm 3^{\circ}\text{C}$, and mix for approximately five minutes. Add the Posaconazole to the vessel in step 5 with constant mixing. Continue mixing until it is fully dispersed. Recirculate the suspension portion from step 6
- 10 through a Microfluidizer, operating at a pressure of about 30,000 \pm 5,000 psi. Process the concentrate until the median of the particles shows a particle size of about $1.4 \pm 0.2 \mu\text{m}$, when measured via laser diffraction techniques that are known in the art.

- When the particle size has been achieved, pass the suspension through the
- 15 microfluidizer and collect in a suitable sized vessel. Add approximately 8-10% of the final batch volume of purified water (at $20 \pm 3^{\circ}\text{C}$) to the feed vessel, and pass through the microfluidizer operating at approximately 30,000 psi. Collect the rinse in the vessel containing the concentrate. Add approximately 22% of the final batch volume of purified water ($20 \pm 3^{\circ}\text{C}$) to the vessel with the concentrate, and mix for
- 20 approximately five (5) minutes. Add the remainder of the polysorbate 80 and simethicone, and mix for approximately five (5) minutes.

Add the sodium benzoate, sodium citrate and citric acid and mix for approximately five (5) minutes. Add the xanthan gum slowly with constant mixing. Continue to mix after addition of the xanthan gum. Allow the xanthan gum to

hydrate without mixing for 30 minutes. Add the glycerin with constant mixing. Add the liquid glucose slowly with constant mixing. Mix for five minutes or until it is dissolved. Add the titanium dioxide and mix using a suitable homogenizer until that ingredient is fully dispersed. Add the artificial cherry flavor, and mix for

5 approximately five minutes. Add purified water at $20 \pm 3^{\circ}\text{C}$, and qs up to a final volume, and mix until a uniform suspension is attained. Collect approximately 20 ml sample for pH measurement and physical observation of the suspension. The pH of the suspension of Example 1 was 5.0.

Example 2

10 Example 2 is another example of a formulation within the scope of the present invention prepared using the procedure of Example 1 and has a pH of 4.5.

<u>Ingredient</u>	<u>Concentration</u> (mg/ml)
Posaconazole (micronized)	40
Polysorbate 80	10
Sodium Citrate, USP,, Monohydrate	0.6
Citric Acid, USP, Monohydrate	1.5
Simethicone, USP	3
Xanthan Gum, NF	3
Sodium Benzoate, NF	2
Liquid Glucose, NF	350
Glycerin, USP	100

Artificial Cherry Flavor	5
Titanium Dioxide	4
Purified Water, USP q.s. ad	1ml

The rate of sedimentation of the liquid suspension of the present invention was determined as set forth below.

TABLE 1

5

**Posaconazole Oral Suspension 40 mg/ml
Rate of Sedimentation**

Bottle Number	Time	Posaconazole mg/ml	% Label Strength	Sodium Benzoate mg/ml	% Label Strength
1	0 min	39.9	99.8	2.00	100
1	5 min	40.0	100	1.99	99.5
1	10 min	40.0	100	2.00	100
1	30 min	40.0	100	2.00	100
1	60 min	40.2	101	2.01	101
1	3 days	40.2	101	2.02	101
2	0 min	39.8	99.5	2.01	101
2	5 min	39.9	99.8	2.00	100
2	10 min	40.2	101	2.01	101
2	30 min	39.8	99.5	1.99	99.5
2	60 min	40.2	101	2.02	101
2	3 days	40.1	100	2.01	101

Two bottles containing the suspension of the present invention were shaken
 10 and left to rest. The bottles were then sampled immediately (time zero), then after
 5 minutes, 10 minutes, 30 minutes, 60 minutes and after 72 hours (three days) post
 shaking. The levels of posaconazole and of the preservative (Sodium Benzoate) in
 these samples were assayed by HPLC. HPLC methods of detection are well-
 known to one of skill in the art.

The results of the assay of the preservative and of the posaconazole remained consistent and did not change. These ranged from 39.8 to 40.2 mg/ml (99.5 to 101%) for the active and 1.99 to 2.02 mg/m: (99.5 to 101%) for the preservative, respectively. The results of this experiment are shown in Table 1
5 above.

The sodium benzoate was not expected to sediment. Surprisingly, the posaconazole was not sedimented after 3 days.

Thus, the compositions of the present invention have both ease of dispersibility and homogeneity as is evidenced by the stability of the samples in
10 Table 1.

Next, accelerated homogeneity testing was performed on the liquid suspension of the present invention.

TABLE 2

**Posaconazole Oral Suspension 40 mg/ml
Homogeneity**

15

Accelerated		Posaconazole	Sodium Benzoate
<u>Condition</u>	<u>Time point</u>	<u>% Label Strength</u>	<u>% Label Strength</u>
Initial	Initial	103;102;104	105;102;103
30 H (30°C/60%RH)	3 Months	103;105;104	103;107;105
RH4 (40°C/75%RH)	3 Months	102;104;103	104;106;106
30 H	6 Months	102;101;102	103;101;102
RH4	6 Months	102;102;102	101;101;102
25 H	12 Months	104;104;104	101;100;100
25 H	24 Months	104;104;104	101;101;101

* Shaking and receiving the dose as per patient instruction.

These data (sedimentation rate experiment) were in agreement with the real
20 time stability data (up to 6 months at 40°C/75%RH and up to 24 months at

25°C/60%RH) that are shown in Table 2. The assay homogeneity results, surprisingly, remained consistently homogenous and practically unchanged.

After 6 months at 40°C/75%RH the homogeneity results ranged from 40.7 to 40.8 mg/ml (101%) for the active and 2.01 to 2.03 mg/ml (101 to 102%) for
5 preservative, respectively. These results were obtained regardless of the portion of the bottle assayed, i.e., top, or bottom of the bottle. Therefore, it can be concluded that the suspension was homogenous throughout the bottle even after relatively long exposure to accelerated stability conditions.

After 24 months at 25°C/60%RH the homogeneity results ranged from 41.5
10 to 41.6 mg/ml (104%) for the active and 2.01 mg/ml (101%) for the preservative, respectively. These results were obtained regardless of the portion of the bottle assayed, i.e., top or bottom of the bottle. Therefore, it can be concluded that the suspension was homogenous throughout the bottle even after long term (24 months) exposure to 25°C/60%RH.

15 Bioavailability is defined as the rate and extent to that the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

C_{max} value is defined as the maximum concentration of the antifungal compound measured (i.e. "peak") in the plasma serum.

20 Formulations of the present invention have the advantage that they have an increased bioavailability and lower variability than previous formulations.

The relative bioavailability of the posaconazole oral suspension was compared to a solid dosage form of posaconazole in healthy subjects.

The first objective was to determine the relative bioavailability of posaconazole given as an oral suspension compared to an oral solid formulation when administered with a high-fat breakfast. The second objective was to determine the effect of high-fat and non-fat food relative to fasting conditions on the oral bioavailability of the compound of formula I when given as an oral suspension.

Twenty healthy subjects completed this randomized, open-label, 4-way crossover, single-dose bioavailability and food effect study of posaconazole. Subjects received each of the following four treatments separated by at least a 7 day washout period:

Treatment A:	200 mg of the compound of formula I in the oral suspension of this invention (5 ml) following a 10-hr. fast
Treatment B:	200 mg of the compound of formula I in the oral suspension of this invention (5 ml) with a standardized high-fat breakfast
Treatment C:	200 mg of the compound of formula I in the oral suspension of this invention (5 ml) with a standardized non-fat breakfast
Treatment D:	2 x 100 mg of the compound of formula I in the tablets (co-precipitate formulation of U.S. Patent No. 5,834,472 with a standardized high-fat breakfast

10

Subjects were randomized to either remain fasted (Treatment A), to receive a standardized high fat breakfast (Treatment B or D) or a standardized non-fat breakfast (Treatment C). Meals were consumed in a 20-minute period prior to the morning drug administration and subjects received the appropriate treatment within 5 minute of completing the breakfast.

15

Blood samples (6 ml) were collected into heparinized tubes for each treatment immediately prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing. Blood was centrifuged at 4°C and plasma stored at or below -20°C until assayed. Plasma concentrations of
5 posaconazole were assayed using a validated high performance liquid chromatographic assay with a LOQ of ng/ml.

Individual plasma concentration-time data were used for pharmacokinetic analysis using model-independent methods. The maximum concentration (C_{max}) and time of maximum concentration (T_{max}) were the observed values. The area
10 under the plasma concentration-time curve from time zero to the final quantifiable sampling time [AUC(tf)] was calculated using the linear trapezoidal method and extrapolated to infinity (I) as follows:

$$AUC(I) = AUC(tf) + \frac{C(tf)}{K}$$

15 where C(tf) is the estimated concentration determined from linear regression at time, tf.

Total body clearance was calculated by the following:

$$CL = \text{Dose} / AUC(I)$$

The apparent volume of distribution (V_{darea/F}) was calculated from the ratio
20 of the total body clearance to the terminal phase rate constant (K).

Summary statistics were calculated for the plasma suspension formulation of the present invention compared to a prior art tablet formulation concentration-time data at each time point and the derived pharmacokinetic parameters. The original

scale and log-transformed C_{max} and AUC values were analyzed using an analysis of variance (ANOVA). The effects due to subject, phase and treatment were extracted.

The plasma concentration-time data and pharmacokinetic parameters for the compound of formula I are tabulated in Tables 3 & 4 and depicted graphically in Figures 1 & 2.

All subjects had 0-hour concentrations on Day 1 reported as below the LOQ (5 ng/ml) except for Subject 20 in Phases 3 and 4 who had quantifiable levels of posaconazole at 0-hour for Treatments B and A of 8.5 and 22.5 ng/ml, respectively. These levels are most likely due to a carry-over effect from accumulation from previous doses.

A summary of the mean^a pharmacokinetic parameters are provided in the table below:

Table 3

Parameter	Unit	Tablet		Suspension					
		High Fat D		10 hr Fast A		High Fat B		Non-Fat C	
		Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
C _{max}	ng/ml	413	33	132	50	512	34	378	43
T _{max}	Hr	5.5	32	5.01	49	4.8	9	4.1	21
AUC(t _f)	ng-hr/ml	10304	41	3553	36	13885	41	9511	38
AUC(I)	ng-hr/ml	11832	39	4179	31	15059	26	10753	35
t _{1/2}	hr	21.0	15	23.5	25	23.0	19	22.2	18

^a: Balanced means, n=20 except for AUC(I) and t_{1/2}, n=15.

Posaconazole was slowly absorbed; the mean T_{max} values ranged from 4.1 to 5.5 hr. Posaconazole was slowly eliminated with a mean terminal t_{1/2} of about 22 hour which was independent of treatment. This study was conducted to evaluate the bioavailability of posaconazole oral suspension (Treatment B) compared to a

tablet formulation (Treatment D), both given with a high-fat food. The results, based on log-transformed data, are shown below:

5

Table 4

Parameter	Treatments Given After High Fat Breakfast	Geometric Mean	Relative Bioavailability ^b (%)	90% Confidence Interval
C _{max}	Suspension Tablet	485 ng/ml 394 ng/ml	123.3	104-146
^a AUC(tf)	Suspension Tablet	13141 ng.hr/ml 9624 ng.hr/ml	136.5	119-156

a: AUC(tf) was used for statistical comparisons because it could be calculated for all treatments for all subjects.

b: Suspension relative to tablet.

On average, the suspension formulation of the present invention resulted in
10 a 23% increase in C_{max} and a 36% increase in AUC(tf) compared to the tablet of the prior art.

The secondary objective of the study was to evaluate the effect of high fat food (Treatment B) and non-fat food (Treatment C) compared to fasting (Treatment A) on the oral bioavailability of posaconazole administered as an oral suspension.

15 The results, based on log-transformed data, are shown below:

Table 5

Parameter	Suspension Treatments	Geometric Mean	Relative Bioavailability (%) ^a	90% Confidence Interval
C _{max} (ng/ml)	High-Fat	485	417	352-493
	Non-Fat	345	296	250-350
	Fast	116	--	--
AUC _(0-t) (ng.hr/ml)	High-Fat	13141	392	343-448
	Non-Fat	8857	264	231-302
	Fast	3352	--	--

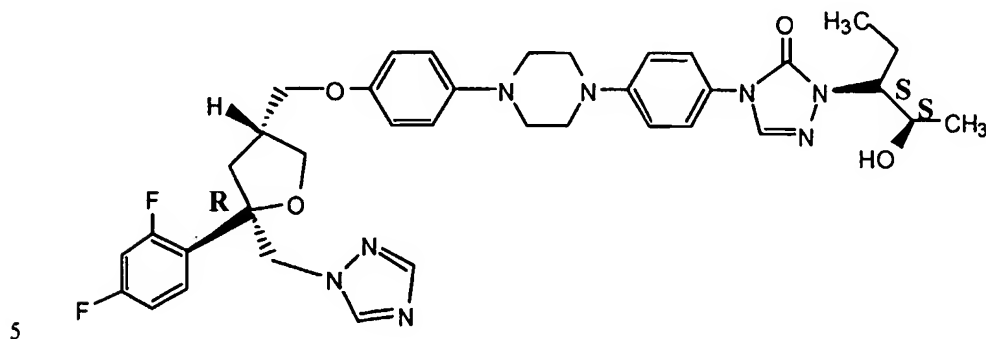
a: Expressed as a percent of Treatment A – Suspension/Fast.

A high fat breakfast produced a 4-fold increase in the bioavailability of posaconazole given in a suspension. This was consistent with results from a previous study where food significantly increased the bioavailability of posaconazole by 3-5-fold for both tablet and capsule formulations. The effect of a non-fat breakfast (Treatment C) compared to fasting (Treatment A) was less, with a 2.5-3-fold increase in bioavailability.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to one skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims along with the full scope of equivalents to which such claims are entitled.

We claim:

1. A liquid suspension comprising an antifungally effective amount of the micronized compound represented by the chemical structural formula I comprising:



at least one thickening agent, at least one non-ionic surfactant, and a pharmaceutically acceptable liquid carrier.

2. The liquid suspension of claim 1, wherein the at least one non-ionic surfactant is a block copolymer of ethylene oxide and propylene oxide, glycol or glyceryl esters of saturated or unsaturated C₈ to C₂₀ acids, polyoxyethylene esters of saturated or unsaturated C₈ to C₂₀ acids, polyoxyethylene ethers of saturated or unsaturated C₈ to C₂₀ acids, polyvinylalcohols or sorbitan esters of saturated or unsaturated C₁₀ to C₂₀ acids.
3. The liquid suspension of claim 1, wherein the at least one non-ionic surfactant is a polyoxyethylene derivative of a sorbitan ester of a saturated or unsaturated C₁₀ to C₂₀ acid.

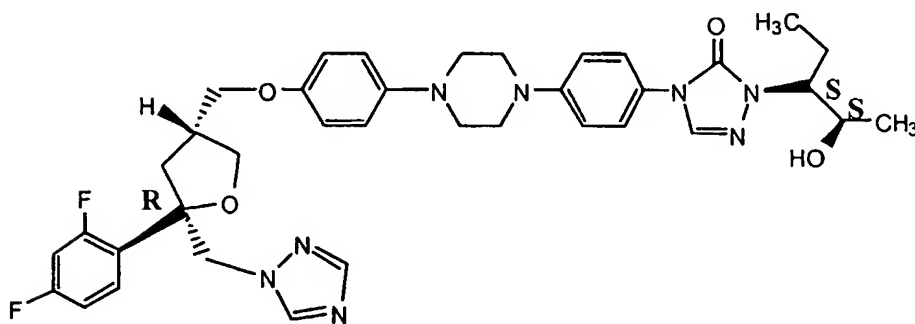
4. The liquid suspension of claim 1, wherein the at least one thickening agent is selected from xanthan gum, liquid sugars, starches, celluloses and mixtures thereof.

5. The liquid suspension of claim 1, wherein a combination of xanthan gum and a liquid sugar are used as the at least one thickening agent.

6. The liquid suspension of claim 1, wherein the micronized compound of formula I has a mean particle size of about 1200 nm to about 1600 nm.

7. A liquid suspension comprising:

- (a) an antifungally effective amount of the micronized compound represented by the chemical structural formula I:

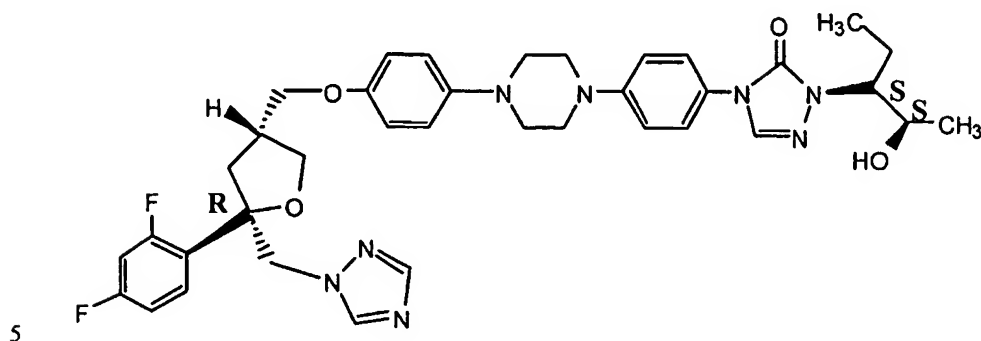


- (b) an effective amount of at least one thickening agent;
- (c) an amount of a buffer system effective to maintain the pH of the system in the range of about 4.0 to about 6.0;
- (d) an effective amount of at least one non-ionic surfactant; and
- (e) a pharmaceutically acceptable liquid carrier.

8. The liquid suspension of claim 7, wherein the at least one non-ionic surfactant is a polyoxyethylene derivative of a sorbitan ester of a saturated or unsaturated C₁₀ to C₂₀ acid.
9. The liquid suspension of claim 7, wherein the sorbitan ester is a fatty acid ester of sorbitan selected from sorbitan monolaurate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, sorbitan monopalmitate, sorbitan monostearate and sorbitan tristearate, or mixtures thereof.
10. The liquid suspension of claim 7, wherein the at least one thickening agent is selected from gums, liquid sugars, starches, cellulose and mixtures thereof.
- 10 11. The liquid suspension of claim 7, wherein a combination of a xanthan gum and a liquid sugar is used as the at least one thickening agent.
12. The liquid suspension of claim 7, wherein a combination of a xanthan gum and a liquid glucose is used as the thickening agent.
13. The liquid suspension of claim 7, wherein the buffer system comprises sodium citrate and citric acid.
- 15 14. The liquid suspension of claim 7, wherein the pharmaceutically acceptable liquid carrier is a combination of purified water, glucose and glycerin.
15. The liquid suspension of claim 7, wherein the micronized compound of formula I has a mean particle size of about 1200 nm to about 1600 nm.

16. A liquid suspension comprising:

(a) an antifungally effective amount of the micronized compound comprising chemical structural formula I:



wherein the micronized compound of formula I has a mean particle size in the range of about 1200 nm to about 1600 nm,

10 (b) an effective amount of a polyoxyethylene derivative of sorbitan esters of saturated or unsaturated C₁₂ to C₁₈ acids;

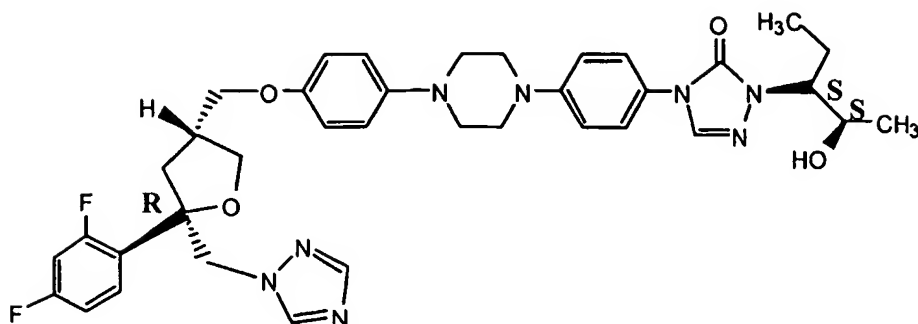
(c) an effective amount of a buffer system sufficient to maintain a pH in the range of about 4.0 to about 6.0;

(d) an effective amount of a combination of two thickening agents,

15 wherein one is a liquid sugar; and

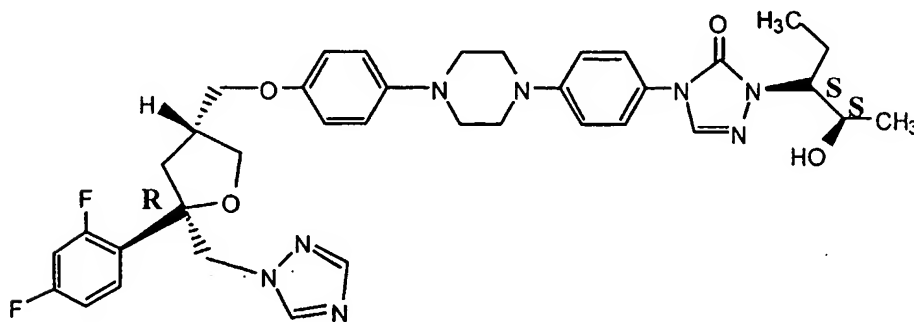
(e) a pharmaceutically acceptable liquid carrier.

17. The use of micronized particles of the compound of chemical structural formula I:



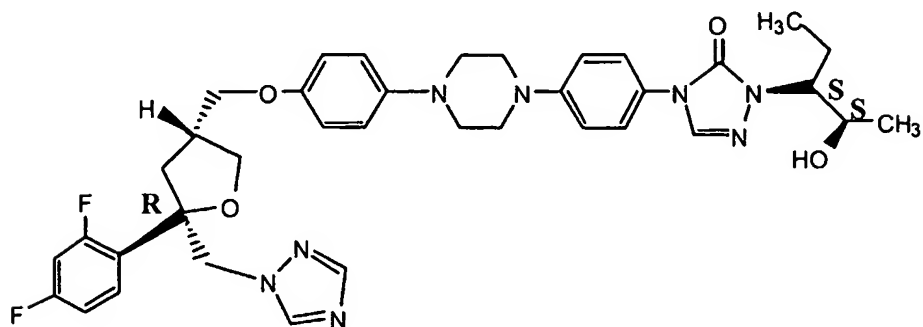
for preparation of a medicament in the form of an oral suspension for the treatment
and/or prevention of a fungal infection in a mammal comprising an antifungally
effective amount of the compound of formula I and at least one thickening agent
5 and a non-ionic surfactant in a pharmaceutically acceptable carrier.

18. A suspension comprising an antifungally effective amount of the micronized
particles of the compound comprising chemical structural formula I:



at least one thickening agent and a non-ionic surfactant in a pharmaceutically
acceptable liquid carrier.

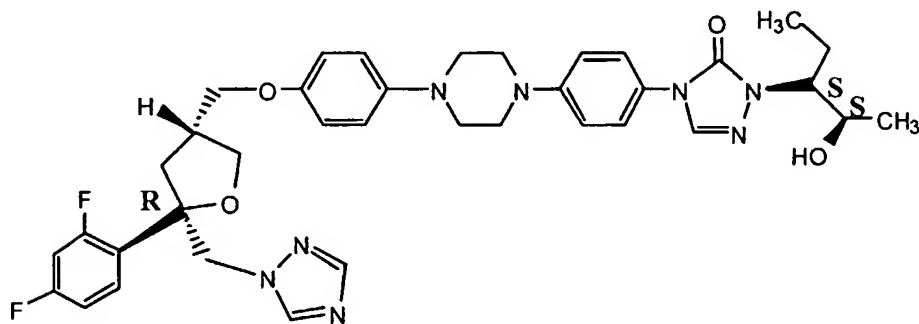
19. A composition of matter comprising micronized particles of the compound represented by structural formula I



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and at least one non-ionic surfactant.

20. A composition of matter comprising micronized particles of the compound represented by chemical structural formula I:



10

in suspension.

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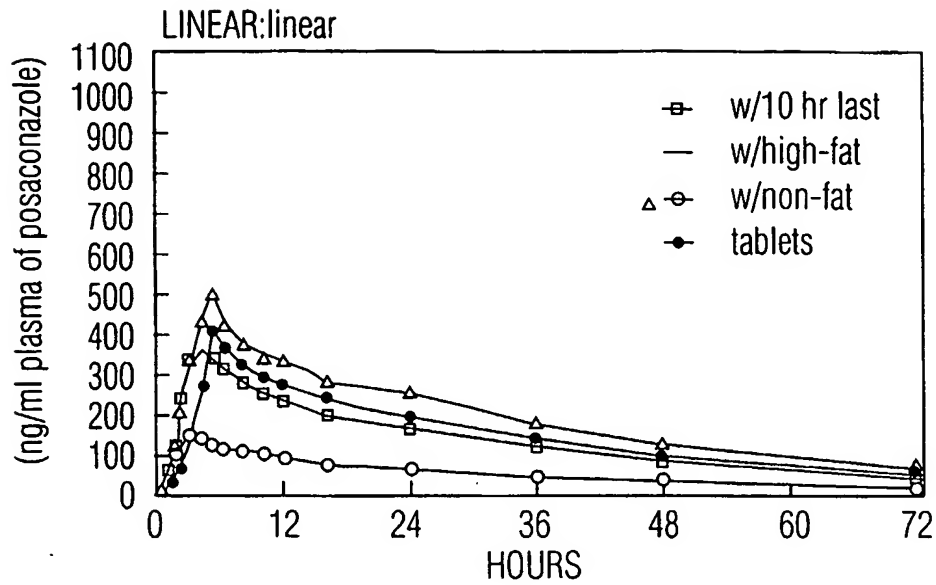


FIG. 1

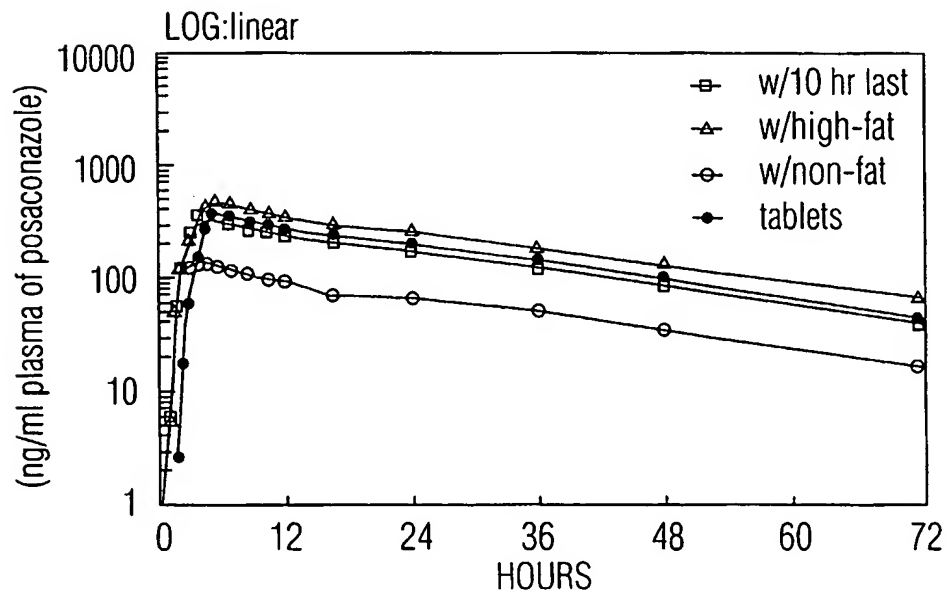


FIG. 2

INTERNATIONAL SEARCH REPORT

Intern: Application No

PCT/us 02/10093

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A01N43/653 A01N25/04 A61K31/496 A61K9/14
 //(A01N43/653,25:04)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 834 472 A (SANGEKAR SURENDRA A ET AL) 10 November 1998 (1998-11-10) column 1, line 33-56 column 3, line 47-67 column 4, line 28-57 column 4, line 62 -column 6, line 23	1-20
Y	---	6,15,16
Y	EP 0 499 299 A (STERLING WINTHROP INC) 19 August 1992 (1992-08-19) page 2, line 4-14 --- -/--	6,15,16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

2 July 2002

Date of mailing of the international search report

31/07/2002

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INTERNATIONAL SEARCH REPORT

Intern Application No
PC1/US 02/10093

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>NOMEIR AMIN A ET AL: "Pharmacokinetics of SCH 56592, a new azole broad-spectrum antifungal agent, in mice, rats, rabbits, dogs, and cynomolgus monkeys." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY., vol. 44, no. 3, March 2000 (2000-03), pages 727-731, XP002204276 ISSN: 0066-4804 the whole document</p> <p>---</p>	1-20
A	<p>SAHA P ET AL: "Effect of solubilizing excipients on permeation of poorly water-soluble compounds across Caco-2 cell monolayers" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 50, no. 3, November 2000 (2000-11), pages 403-411, XP004257220 ISSN: 0939-6411 the whole document</p> <p>---</p>	1-20
A	<p>WO 95 17407 A (SCHERING CORP ;SAKSENA ANIL K (US); GIRIJAVALLABHAN VIYYOOR M (US)) 29 June 1995 (1995-06-29) cited in the application the whole document</p> <p>-----</p>	1-20

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/US 02/10093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5834472	A	10-11-1998	NONE
EP 0499299	A	19-08-1992	US 5145684 A 08-09-1992
		AT 184202 T 15-09-1999	
		AT 195416 T 15-09-2000	
		AU 642066 B2 07-10-1993	
		AU 1014592 A 30-07-1992	
		AU 654836 B2 24-11-1994	
		AU 1014792 A 30-07-1992	
		CA 2059431 A1 26-07-1992	
		CA 2059432 A1 26-07-1992	
		DE 69229925 D1 14-10-1999	
		DE 69229925 T2 17-02-2000	
		DE 69231345 D1 21-09-2000	
		DE 69231345 T2 26-04-2001	
		DK 498482 T3 27-03-2000	
		DK 499299 T3 02-01-2001	
		EP 0498482 A2 12-08-1992	
		EP 0499299 A2 19-08-1992	
		ES 2139586 T3 16-02-2000	
		ES 2149164 T3 01-11-2000	
		FI 920321 A 26-07-1992	
		FI 920322 A 26-07-1992	
		GR 3032059 T3 31-03-2000	
		HU 62462 A2 28-05-1993	
		HU 60635 A2 28-10-1992	
		IE 920217 A1 29-07-1992	
		IE 920218 A1 29-07-1992	
		IL 100754 A 16-10-1996	
		IL 100755 A 08-12-1995	
		JP 4317053 A 09-11-1992	
		JP 4295420 A 20-10-1992	
		KR 200061 B1 15-06-1999	
		MX 9200291 A1 01-10-1992	
		MX 9200292 A1 01-10-1992	
		NO 920333 A 27-07-1992	
		NO 303668 B1 17-08-1998	
		NZ 241361 A 25-06-1993	
		NZ 241362 A 25-06-1993	
		PT 499299 T 31-01-2001	
		SG 55104 A1 21-12-1998	
		RU 2074002 C1 27-02-1997	
		RU 2066553 C1 20-09-1996	
		US 5451393 A 19-09-1995	
		US 5494683 A 27-02-1996	
		US 5552160 A 03-09-1996	
		US 5399363 A 21-03-1995	
		US 5318767 A 07-06-1994	
WO 9517407	A	29-06-1995	AT 204875 T 15-09-2001
		AU 681753 B2 04-09-1997	
		AU 1512795 A 10-07-1995	
		CA 2179396 A1 29-06-1995	
		CN 1142828 A ,B 12-02-1997	
		CZ 9601805 A3 15-01-1997	
		DE 69428125 D1 04-10-2001	
		DE 69428125 T2 02-05-2002	
		DK 736030 T3 29-10-2001	

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INTERNATIONAL SEARCH REPORT

Intern. application No
PCT/US 02/10093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9517407 A	EP	0736030 A1	09-10-1996
	ES	2159623 T3	16-10-2001
	FI	962577 A	20-06-1996
	HU	75879 A2	28-05-1997
	JP	2834889 B2	14-12-1998
	JP	9500658 T	21-01-1997
	KR	179990 B1	20-03-1999
	NO	962616 A	07-08-1996
	NZ	278713 A	19-12-1997
	PL	315169 A1	14-10-1996
	PT	736030 T	30-01-2002
	SK	82696 A3	05-03-1997
	WO	9517407 A1	29-06-1995
	US	5714490 A	03-02-1998
	US	5703236 A	30-12-1997
	US	5693626 A	02-12-1997
	US	5710154 A	20-01-1998
	US	5703079 A	30-12-1997
	US	5661151 A	26-08-1997
	ZA	9410142 A	02-05-1996
